약학석사 학위논문

Evaluation of Prescribing Errors Related to Computerized Physician Order Entry System: A Systematic Review and Meta-analysis

체계적 문헌고찰과 메타분석을 통한 전산처방자동화시스템과 관련된 처방오류 평가 연구

2020 년 8 월

서울대학교 대학원

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2020 년 7 월

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Abstract

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Computerized Physician Order Entry (CPOE) systems and Clinical Decision Support Systems (CDSS) have been proven to contribute to improve patient's safety and quality of care; however, the adoption of computerization introduced a new type of error, called "system-related" or "technology-induced" errors. A comprehensive evaluation regarding the prevalence of CPOE-related errors (CRE) is lacking. The aim of this study was to describe the prevalence of CRE evaluated by pharmacists and to evaluate the association between the introduction of CPOE and prescribing errors.

A systematic review and meta-analysis were conducted of studies retrieved from the MEDLINE, Embase, Cochrane, and Scopus up to March 2020. All studies reporting the rate of prescribing errors related to CPOE were included. The prevalence

of CRE among overall prescribing errors occurred in the hospitals was estimated using pooled prevalence estimate with a 95% confidence interval (CI) and relative risk (RR) was calculated for the subgroup analysis.

A total of 14 studies were identified and included in the systematic review and meta-analysis. In the meta-analysis of 13 data of estimate, the overall pooled prevalence of CRE across studies were 32.36% (95% CI 22.87 - 42.62). Among the 6 types of error identified throughout the studies: omission, wrong drug, wrong dose, wrong route/form, wrong time, and monitoring error, the main type of error related to CPOE were wrong dose (47.28%, 95% CI 38.38-56.26), followed by wrong drug (14.45%, 95% CI 7.96-22.40). The subgroup analysis revealed that the risk of error was not significantly reduced with CPOE (RR 0.842, 95% CI 0.559 - 1.268), except omission which was significantly reduced after the implementation of CPOE (RR 0.484, 95% CI 0.282 - 0.831).

Our study findings support that system-related errors were a major reason for CPOE not delivering a significant reduction in the overall rate of clinical errors. A considerable risk for prescribing errors still exists, which healthcare professionals should be aware that CPOE could also lead to a new type of medication errors. In order to reduce the prescribing error related to CPOE, the system should be continually examined and users should receive periodic and multidisciplinary training on the use of CPOE and CDSS.

Keywords : computerized physician order entry system, prescribing error, pharmacist
Student Number : 2018-21399

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Ⅰ. Introduction

1.1. Study Background

Healthcare quality and patient safety have been major target of improvement for past decades. Medication error results in 2 – 5% of all hospital admissions worldwide [1] and injures about 1.3 million patients annually in United States alone [2]. Although only small percentage of medication error actually results in adverse drug events, seven percent of medication error-related harm are severe [1]. It also prolongs hospital stays by 1.7 to 4.6 days, which increases additional costs to the healthcare system. The cost associated with medication errors has been almost 1% of total global health expenditure [2]. Medication errors occur in 5% of prescriptions, mostly due to prescribing error [3-5]. Approximately, 25% of these error incidents are preventable [1]. As one of the strategies to prevent the prescribing errors, various health information technologies were introduced to reduce these kinds of error and improve patient safety.

The Computerized Physician Order Entry (CPOE) systems allow physicians to prescribe patient services electronically. The Clinical Decision Support Systems (CDSS) are designed to provide physicians with real-time, evidence-based decision supports, such as automatic dose modification in renal or hepatic failure, and detection of drug interactions, as they enter medication orders and check for a wide variety of potential errors. CPOE-CDSS bundle have been proven to contribute to improve patient's safety and quality of prescription [6-9]. It has been shown to reduce medication errors, mainly at the prescribing stage [10]. Previous

studies highlighted the effectiveness of CPOE, such as a decrease in prescribing errors and adverse drug events, the elimination of illegibility, and improvements to traceability [11–14]. Nevertheless, it is now well recognized that the adoption of computerization has induced or contributed unintended consequences, which have been labeled as "system–related" or "technology–induced" errors [15]. An increasing number of publications have reported the appearance of these errors [16–18]. However, the prevalence of system–induced errors is controversial: some researchers have suggested that CPOE contributes very little to the overall rate of medication errors (0.1–0.3%) [19], but others have found that 17.1% of all medication incidents were technology–based and of these more than 60% are related to CPOE [9]. Therefore, a research is needed to quantitatively present the error burden of CPOE–related errors on the overall rate of prescribing error.

1.2. Purpose of Research

In order to capture the snapshot views on prevalence of CPOE–related errors (CRE) published so far, we performed a systematic review and meta–analysis to describe the prevalence of CRE and to evaluate the association between the introduction of CPOE and rate of prescribing errors.

Ⅱ. Methods

2.1. Search Strategy and Data Sources

We conducted a comprehensive systematic review of the literature in accordance with the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix A) [21], using the following databases for studies published up to March 2020: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Scopus. No restriction was imposed in terms of study design and publication language. The articles in foreign languages other than English and Korean were translated using Google Translation website. Additionally, the references cited in selected articles were also reviewed to include any relevant publications. The following search terms were used: 'computerized physician order entry system', 'prescribing error', and 'pharmacist' (Appendix B). The search term "pharmacist" was used to confine a group of healthcare professionals to pharmacist in order to give uniformity in defining errors. A designated researcher (GHP) identified the articles according to the search strategy described above.

2.2. Eligibility Criteria and Study Selection

Studies meeting the following selection criteria were included in this systematic review and meta-analysis: studies that included participants of any age admitted to the hospital, studies that reported the number of errors specifically related to CPOE, and

studies where pharmacists either identified or intervened prescribing errors. The following studies were excluded: non-original research article types (letters, commentaries, case reports, reviews or conference abstracts), outpatient setting, studies involved other health information technologies, and studies reporting non-related outcomes, inappropriate comparison, and studies with no access to their full-text articles.

One researcher (GHP) searched the related articles according to the search strategy, and a second researcher (EL) confirmed the search process. After removing duplicates, two researchers (GHP and SKS) independently selected studies by reviewing the titles, abstracts, and full texts, based on the aforementioned eligibility criteria. Any disagreements between the reviewers were resolved by consensus involving the participation of the third investigator (EL).

2.3. Data Extraction and Quality Assessment

The following information was extracted using a standardized form: country, year of publication, study design, type of hospital, departments, study duration, name of CPOE software, and stage of CDSS, period after CPOE implementation, and classification used to identify CRE. Most of the studies we came across identified errors using medical records. One author (GHP) extracted the quantitative prescribing errors related to CPOE, as reported in the individual studies. The prevalence of CRE was calculated as the number of CRE divided by the total number of prescribing errors. One of the authors (GHP) standardized the taxonomy of the reported prescribing errors of the various studies by adapting the National

Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) taxonomy [22] and the taxonomy developed by Abdel-Qader [23], grouping into "omission", "wrong drug", "wrong dose", "wrong route/form", "wrong time", "wrong patient", and "monitoring error" categories. Developed taxonomy of error and examples were outlined in Appendix C. If the original authors classified more than one types of error into one category in the results, those data were excluded in this analysis because they did not fit into our classification.

For quality assessment, modified Newcastle-Ottawa Scale (NOS) [24] and Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [25] were used for observational studies and pre-post studies, respectively. The NOS uses a star system to assess the quality of a study, based on selection and comparability of the groups, ascertainment of exposure, and assessment of outcome; the quality of the study was rated as poor (0-3 stars), fair (4-6 starts), or good (7-9 stars). The ROBINS-I tool, comprising of seven domains, was used; each domain was assessed low, moderate, serious, critical, and no information of bias: (1) bias due to confounding, (2) bias in selection of participants into the study, (3) bias in classification of interventions, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) bias in selection of the reported result. Two authors (GHP and SYS) evaluated the quality of the selected studies, and any disagreements were resolved through a discussion with the third investigator (EL).

2.4. Statistical Analysis and Heterogeneity

The primary analysis focused on assessing the prevalence of CPOE-related errors among overall prescribing errors and their types. When each study reported data from multiple independent subgroups, we treated each subgroup as a separate study, following the suggested analytic approaches in the literature [26]. To provide a more accurate estimate of CRE rates that was adjusted for study sample size, we calculated pooled prevalence estimates and 95% confidence interval (CI) of the mean CRE rate using the random effects models for each denominator to assess the variability within and between studies. In a meta-analysis of the prevalence, when estimate for a study tends toward either 0% or 100%, the variance for that study moves towards zero and as a result its weight is overestimated. Therefore, we conducted the meta-analysis with double arcsine transformation, which stabilized the variance by making variance dependent only on the sample size. The final pooled result and 95% CIs were back-transformed for ease of interpretation [27]. For the subgroup analysis, comparing incidences of prescribing error before and after the implementation of CPOE, relative risks (RR) were calculated using proportion of CRE reported in each study. The meta-analyses were performed using MetaXL version 2.0 software (EpiGear Int Pty Ltd, Wilston, Australia) and Comprehensive Meta-analysis, version 2 (Biostat, Englewood, NJ, USA).

Heterogeneity among studies was evaluated by Cochrane Q test and I^2 statistical methods. A significant value ($P < 0.10$) in Cochrane Q test verified the presence of heterogeneity and value of I2 statistics was used to measure the amount of heterogeneity between studies. Since I^2 provided the percentage of variability due

to the heterogeneity rather than change difference or sampling error, I2 > 75% was considered statistically significant heterogeneity [28]. Therefore, we applied either the fixed effects model or the random effects model, depending on the significance of heterogeneity (P <0.10 and I^2 ≥ 75%). Publication bias was assessed using the funnel plot, doi plot, and Luis Furuya-Kanamori asymmetry index (LFK index). In the presence of symmetry, one can concluded as no publication bias, but in the absence of symmetry, one can expect publication bias. An LFK index within ±1, out of ±1 but within ±2, and > ± 2 was to mean no asymmetry, minor asymmetry and major asymmetry, respectively [29]. To estimate the publication bias of subgroup analysis, we created a funnel plot by plotting the natural logarithm of the RRs against the standard error and symmetry of the funnel plot was assessed with Egger's test. The possibility of publication bias was assessed by visual inspection of funnel plot using Egger's test [30].

Ⅲ. Results

3.1. Literature Search

A total of 1,255 articles were identified by searching the four electronic databases using keywords, as well as the relevant reference sections. After removing duplicates, 840 records remained, and of those, 55 articles were selected for full-text review. After the full-text review, 41 articles were excluded due to the reasons summarized in Figure 1. We excluded studies that did not report the number of prescribing errors generated using CPOE as their outcome. Due to the recognized under-reporting of errors in the voluntary reports [31-33], we only included studies with the interventions after reviewing orders or the observation to detect the prescribing errors. The remaining 14 studies were included in the final meta-analysis. They were 7 prospective, 3 retrospective, and 4 pre-post studies published between 2007 and 2019.

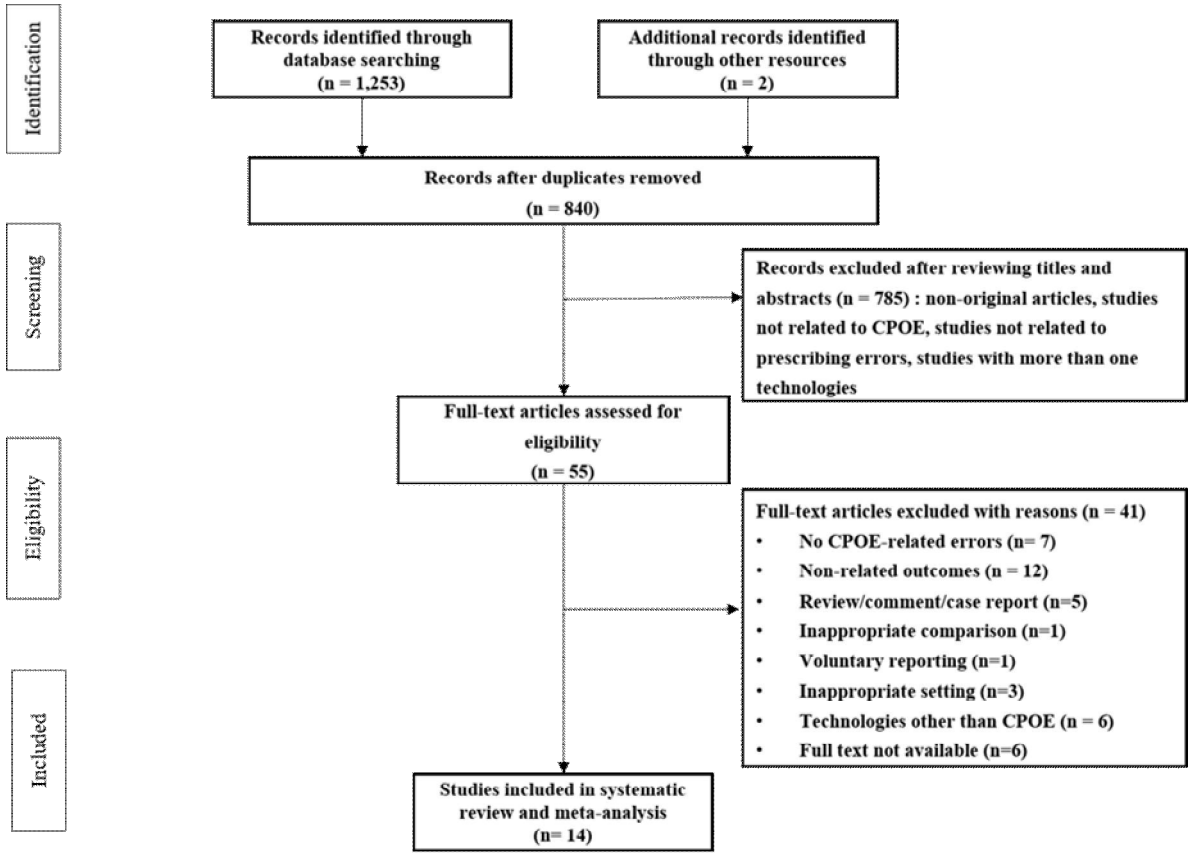

Figure 1. Flow chart of study selection process

3.2. Study Characteristics and Quality

The majority of the observational studies included in our review were conducted in a number of European countries, including France, Spain, United Kingdom and Australia. The range of study duration was between 5 days to 3 years. Studies were carried out in the geriatric, pediatric, psychiatric, intensive care, medical, and surgical departments. Nine studies measured primary outcomes in the number of errors and 5 studies counted prescribing errors with the pharmaceutical interventions. Nine studies provided their definitions of prescribing error and 11 studies provided their definition of CPOE-related errors. Identification of prescribing error and CRE was depended on researchers' judgement for those did not provide the definitions. Authors from 6 studies developed their own taxonomy to classify prescribing errors and 7 studies classified prescribing errors based on a published taxonomy: The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP, n=2) and the French Society of Clinical Pharmacy (SFPC, n=5). Four studies performed an inter-reliability analysis using kappa score to determine the consistency between researchers. Loustalot et al. [38] had weekly pharmaceutical staff meeting to discuss rationales of interventions made during the week to standardize practices between pharmacists, pharmacy residents, and students to sustain the consistency. The characteristics of these 14 studies included in the meta-analysis are summarized in Table 1.

With the respect to the quality assessment, five studies were considered as good quality, four studies of fair quality, and one poor quality due to the insufficient description on definitions of

prescribing error or CRE. Detailed information regarding the quality assessment was described in Appendix D.

The risk of bias of four pre-post intervention studies using ROBINS-I tool was displayed in Figure 2. All four studies showed a low probability of bias in five domain: (1) bias due to confounding, (2) bias in selection of participants into the study, (3) bias in classification of interventions, (4) bias due to deviations from intended interventions, (5) bias in selection of the reported result. Other than Armada et al [35], which had some missing data on the number of errors, the remaining three studies were not likely to be biased due to the missing data. However, the risk of bias was rated "serious" or "moderate" in the measurement of outcome in the studies due to the subjectivity in identifying and classifying errors.

Table 1. Characteristics of included studies

Study	Country	Study design	Type of hospital, departments	Study duration	Name of CPOE systems, CDSS stage[a]	Post-CPOE implementation	Classification of CRE
Abdel-Qader *et al.* (2010) [23]	United Kingdom	Retrospective study	Teaching hospital, Medical and Care of the Elderly	4 weeks	iSoft Clinical Manager, none	8 years	Taxonomy developed by the author
Alhanout *et al*[b] (2017) [34]	France	Retrospective study	N/A, pediatric department	6 months	Pharma®, none	N/A	N/A
Armada *et al.* (2014) [35]	Spain	Pre-post study	Tertiary care university center, cardiac intensive care unit	7 months	Farma Tools® Dominion, basic	3 months	NCCMERP taxonomy
Bouchand *et al.* (2007)[18]	France	Pre-post study	Cochin University Hospital, Internal medicine department	54 weeks	Phedra®, Actipidos®, basic	N/A	Taxonomy developed by the authors
Estellat *et al*. (2007) [36]	France	Prospective study	Georges Pompidou European Hospital, 2 surgical and 8 medical wards	5 days	Dx-Care®, basic	5 years	Taxonomy developed by the authors
Hellot-Guersing *et al*.[b] (2016) [37]	France	Prospective study	Lucien-Hussel Hospital Center, Medical, surgical, obstetric wards	4 years	Disporao® and Orbis®, none	5 years	French Society of Clinical Pharmacy
Loustalot *et al.* (2019) [38]	France	Prospective study	Tertiary care teaching hospital, entire hospital	13 months	DxCare® Medasys, basic	15 years	French Society of Clinical Pharmacy
Raimbault-Chupin *et al.* (2013) [39]	France	Prospective study	Angers University Hospital, geriatric acute care unit	6 months	Crossway®, none	N/A	French Society of Clinical Pharmacy

Rouayroux *et al.* (2019) [40]	France	Retrospective pre-post study	Toulouse University hospital, cardiology and diabetology departments	3 years	Orbis ME®, none	1 year	French Society of Clinical Pharmacy
Velez-Diaz *et al.*[b](2017) [41]	Spain	Prospective study	University hospital, geriatric department	6 months	Prescriwin®, advanced	6 years	Taxonomy developed by the authors based on Westbrook [41], Magrabi [47] and NCCMERP taxonomy
Vialle *et al*[b] (2011) [42]	France	Prospective study	La Roche-Sur-Yon hospital, several units including obstetric surgery department	1 year	Genois®, basic	1 year	French Society of Clinical Pharmacy
Villamanan *et al.* (2013) [43]	Spain	Prospective study	Tertiary care teaching hospital, entire hospital	1 months	N/A, basic	3 years	NCCMERP taxonomy
Westbrook *et al.* (2012) [44]	Australia	Pre-post study	2 teaching hospitals, hospital A: 2 geriatric, renal/vascular, respiratory wards, hospital B: psychiatry, cardiology	Hospital A: 8 months Hospital B: 23 months	Hospital A: Cerner®, basic Hospital B: iSoft MedChart®, advanced	Hospital A: 28 weeks Hospital B: 16 weeks/10 weeks	Taxonomy developed by the authors
Westbrook *et al.* (2013) [45]	Australia	Prospective study	2 teaching hospitals, geriatric, psychiatry, cardiology	18 weeks	Hospital A: Cerner Millennium, none PowerOrder® Hospital B: CSC MedChart, none	6 months	Taxonomy developed by the authors

CPOE: Computerized Physician Order Entry, CDSS: Clinical Decision Support System, CRE: computer-related error, N/A: not applicable, CPOEMS: Computerized Prescriber Order Entry Medication Safety, NCCMERP: National Coordinating Council for Medication Error Reporting and Prevention

[a] Categorized as basic and advanced according to Kuperman et al.[46]

[b] Not included in the subgroup analysis

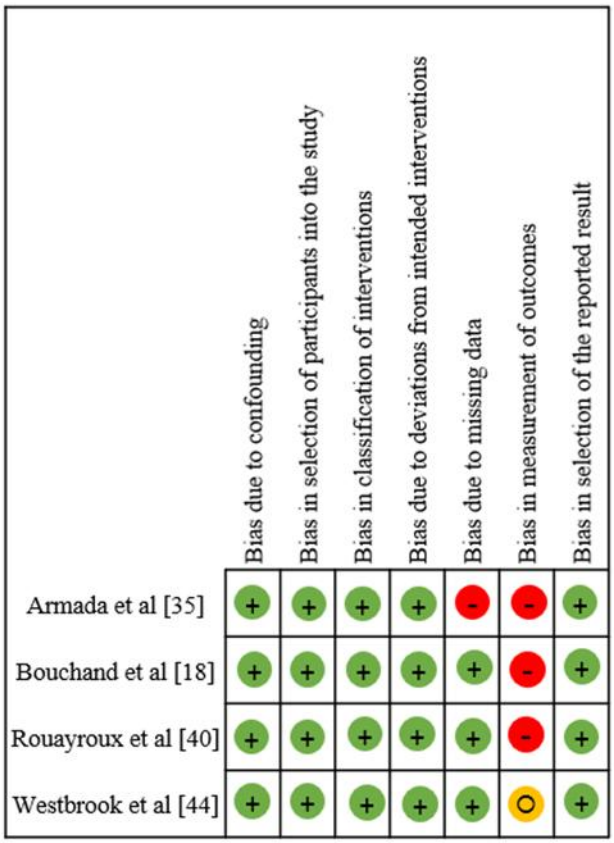

Figure 2. Risk of bias in the included non-randomized studies-of interventions

3.3. Meta-analysis

3.3.1. Prevalence of CRE

The findings of the meta-analysis were summarized in Figure 3. Ten studies provided 13 data points suitable for a meta-analysis with the prevalence of CRE outcomes. Four studies [34,34,41,42] were not included in the analysis since they only reported the error rate per CRE types. The prevalence of each study ranged from 12.78% to 58.54% with a substantial heterogeneity across the studies (Cochrane Q=832; $p < 0.001$; I2=99%). Both the funnel plot (Fig. 4) and the Doi plot (Fig. 5) showed minor asymmetry indicating the presence of bias (LFK index = −1.35). The most likely explanations for the asymmetry were selection bias, including publication bias, or true heterogeneity in the included studies [48]. The overall random-effects pooled prevalence of CRE across the studies were 32.36% (95% CI 22.87 – 42.62). Among the CRE, the main type of error related to CPOE were wrong dose (47.28%, 95% CI 38.38-56.26) and another important source of error was wrong drug (14.45%, 95% CI 7.96-22.40). Table 2 shows the prevalence of the CRE by types.

Table 3 presented an overview of the common causes drawn from 11 studies. The mechanisms responsible for the CRE were related to the ergonomy of the computer, alerts, and misuse of CPOE.

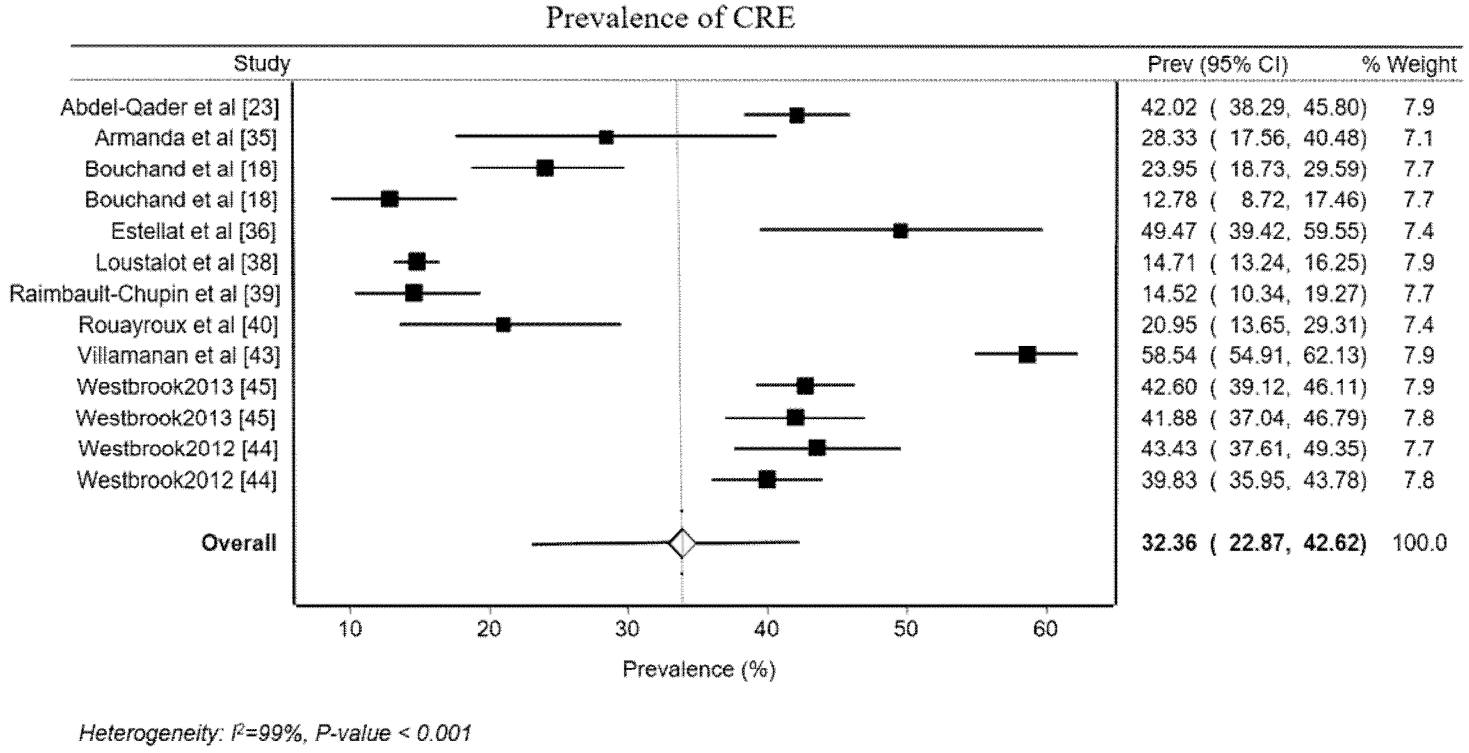

Figure 3. Forest plots of prevalence of CRE. CRE, CPOE-related errors.

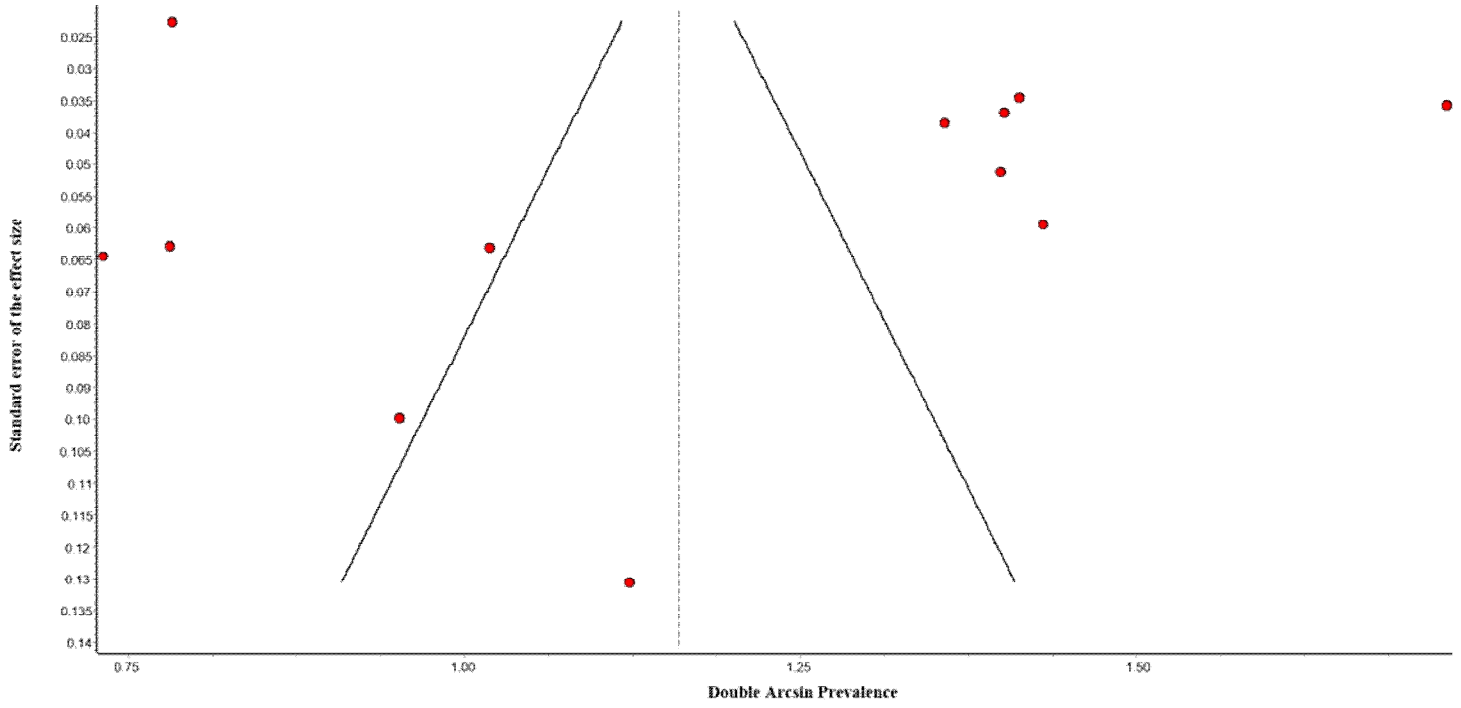

Figure 4. Funnel plot of publication bias of the prevalence of CRE. CRE, CPOE-related error

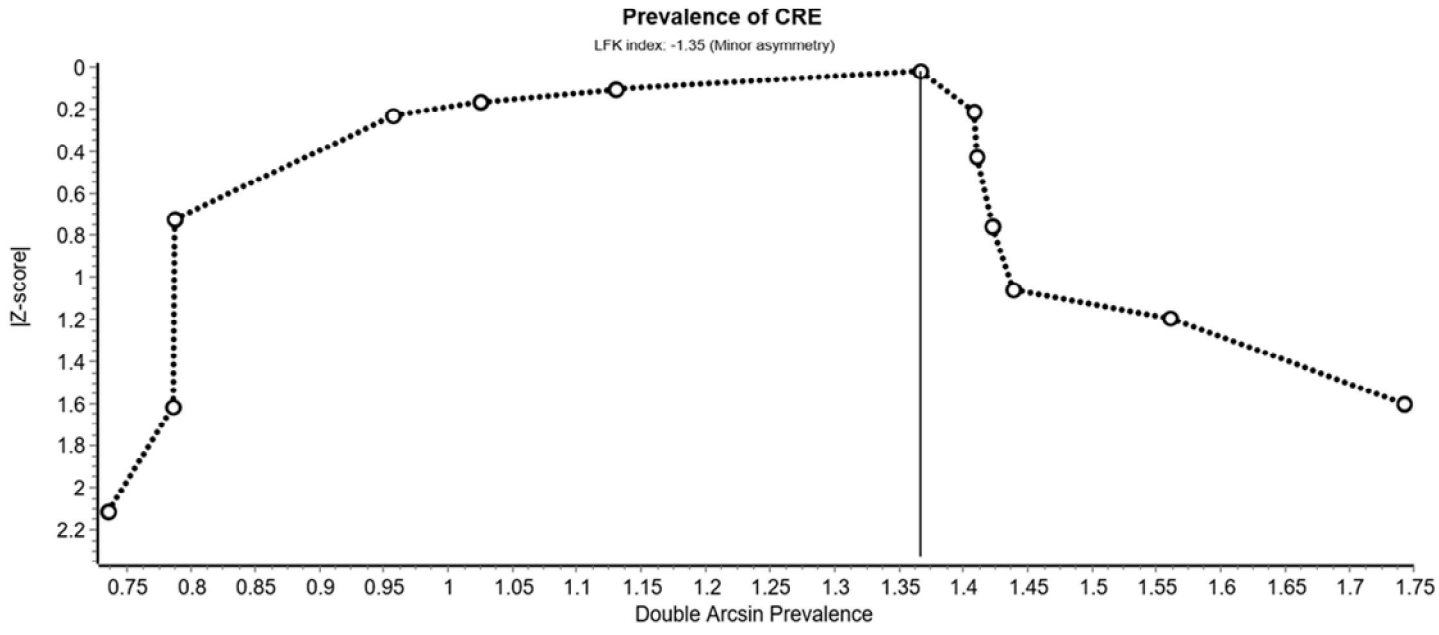

Figure 5. Doi plot of publication bias of the prevalence of CRE. CRE, CPOE-related error.

Table 2. Prevalence evaluation by CRE types

	Prevalence by CRE types		
	Number of included studies[a]	**Pooled prevalence, % (95% CI)**	**I^2, %**
Omission	6	9.53 (0.00 − 24.24)	98.7
Wrong drug	13	14.45 (7.96 − 22.40)	97.5
Wrong dose	13	47.28 (38.38 − 56.26)	96.8
Wrong route/form	10	9.80 (4.75 − 16.30)	96.6
Wrong time	9	11.04 (3.53 − 21.57)	98.5
Monitoring error	1	3.31 (1.55 − 5.67)	0

[a]Studies excluded if classification of error did not match

Table 3. Common causes of CRE reported in the studies

Computer ergonomics [18,34,38-40,42,43]
• Improper selection from a drop-down menu • Typographical error • Difficulties in viewing the entire prescription from the screen
Alert [18,35,38,41,42,44]
• Alert fatigue • Lack of alert (i.e. look-alike sound-alike warning)
Misuse of CPOE[18,37,39,41-44]
• Incorrect use of special interface • Autocomplete features • No/wrong entry into the system • Failure to modify pre-defined orders or system default regimen • Failure to modify previous prescription • Complex prescription (i.e. tapering steroid) • Discrepancies in the free-text field

3.3.2. Incidence of CRE

Further subgroup analysis was conducted by each type of error to compare overall error rate before and after CPOE implementation (Fig. 6). Three pre-post studies [18,40,44] were included and multiple control groups from the study were treated independently in the meta-analysis. Overall, the risk of error was not significantly reduced with CPOE (RR 0.842, 95% CI 0.559 - 1.268, p = 0.410). A random effects model was applied due to the statistical significance of heterogeneity across the studies (I^2=90.28%, P=0.293). Among 5 types of CRE accessible from the included studies, only omission was significantly reduced after the implementation of CPOE (RR 0.484, 95% CI 0.282 - 0.831, p < 0.05). The impact of the publication bias on the integrated estimate of this analysis was shown to be not significant. Egger's regression test (P = 0.49) was not statistically significant, indicating the symmetry of the funnel plot (Fig. 7). In pre-post studies, wrong route/form was the highest in rate (56.45%), followed by wrong dose (42.27%) (Table 4). Total numbers of error were different by types due to the difference in the number of included studies. We were only able to extract data for 'omission' and 'wrong dose' from Bouchand et al [18].

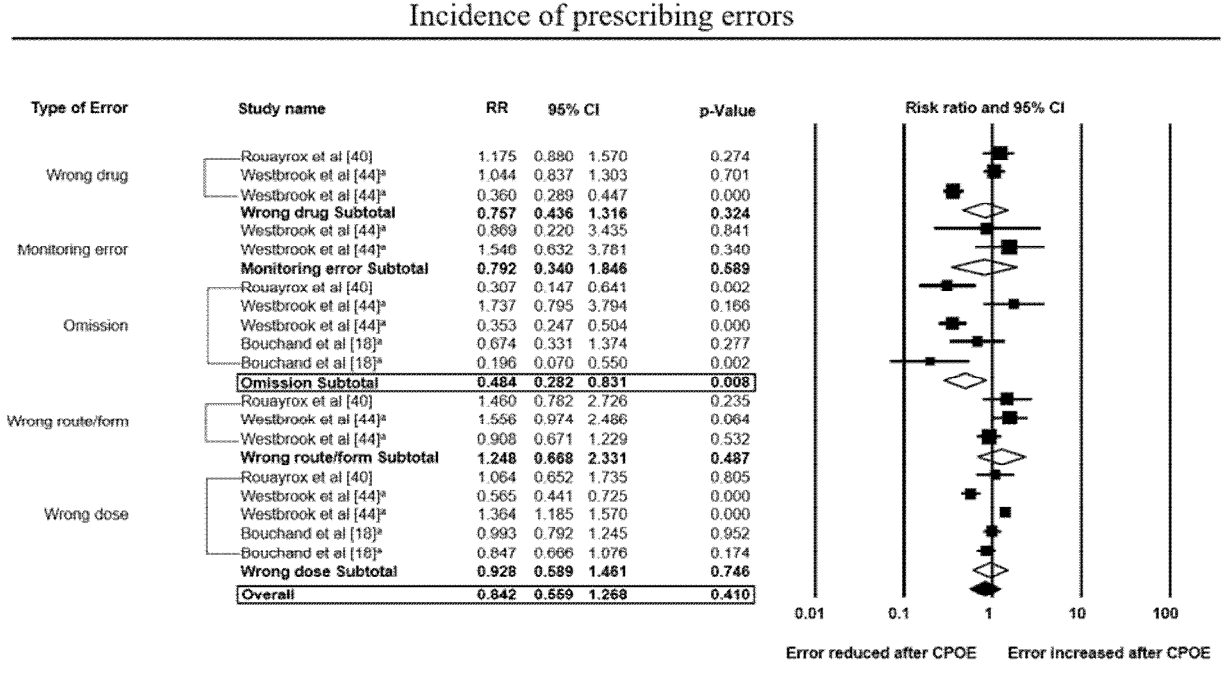

Figure 6. Forest plot of incidence of prescribing error after implementation of CPOE compared with that of before implementation of CPOE

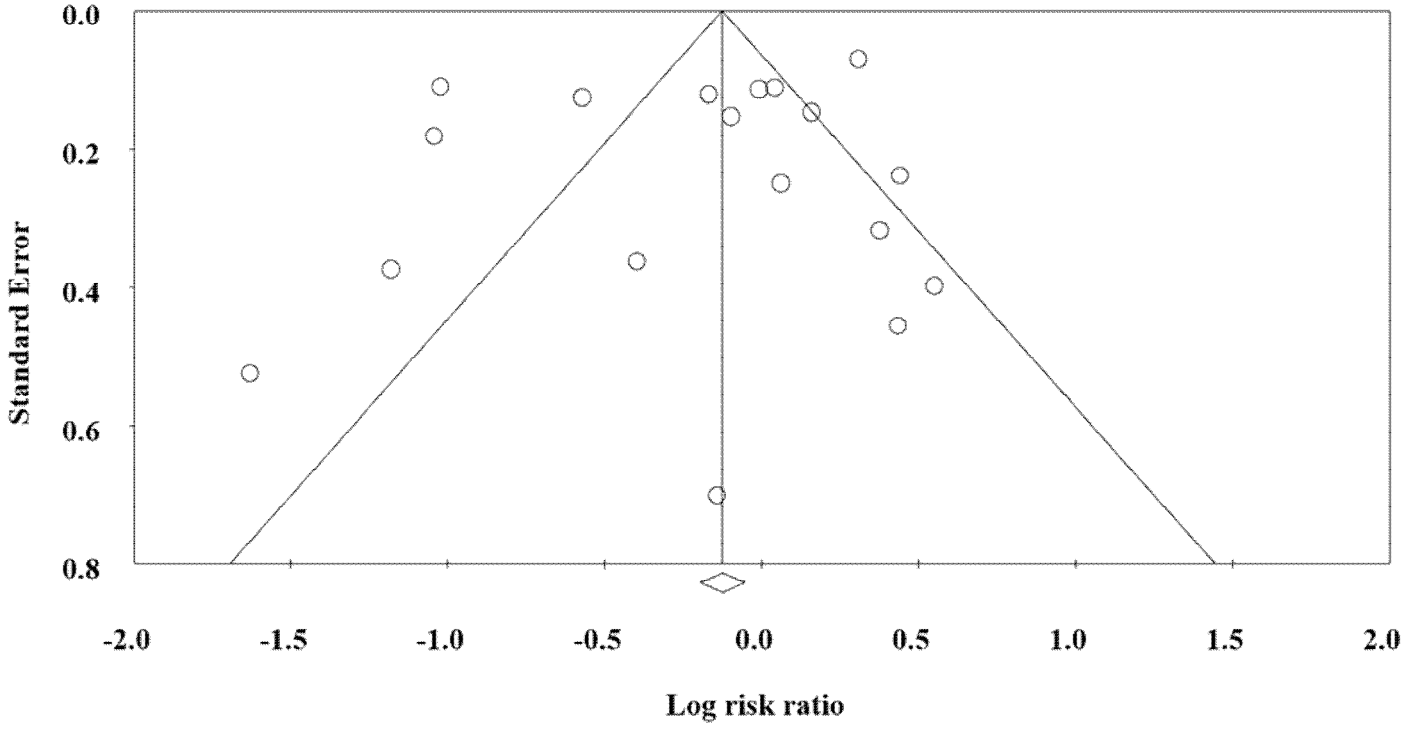

Figure 7. Funnel plot of publication bias of the association between the introduction of CPOE and the rate of prescribing errors

Table 4. Incidence evaluation by CRE types

Error Category	Number of errors in pre period (%)	Number of errors in post period (%)	Number of computer-related errors (%)
Omission[a]	199/1307 (15.22)	84/1447 (5.81)	8/84 (9.52)
Wrong drug[b]	446/1198 (37.23)	237/982 (24.13)	53/237 (22.36)
Wrong dose[a]	486/1307 (37.18)	563/1447 (38.91)	238/563 (42.27)
Wrong route/form[b]	134/1198 (11.19)	124/982 (12.63)	70/124 (56.45)
Monitoring error[b]	27/1198 (2.25)	18/982 (1.83)	0/18 (0)

[a]3 studies included: Rouayroux et al. [40], Westbrook et al. [44], Bouchand et al. [18]
[b]2 studies included" Rouayroux et al. [40], Westbrook et al. [44]

Ⅳ. Discussion

CPOE are widely viewed as crucial for reducing prescribing errors, however, the implementation of this technology introduced new types of error that did not occur in the traditional medication ordering system. Our study found 32.26% error rate of CPOE out of all medication errors that occurred at the prescribing phase. Among 7 types of CRE we defined, we were able to collect data for 6 types including omission, wrong drug, wrong dose, wrong route/form, wrong time, and monitoring error. The most frequent errors were wrong dose and wrong drug with the prevalence of 47.28% and 14.45%, respectively. The common causes of CPOE errors described by the authors could be categorized as computer ergonomy, alerts, and the misuse of the system. The 'wrong dose' was the most frequent error reported likely because it can arise from multiple errors: wrong strength, frequency, unit, and quantity.

Similarly, the 'wrong drug' error not only results in giving the wrong drug, but may also result from drug-drug interaction, contraindication or undetected drug allergy or adverse drug reaction. In this context, CDSS can contribute to decrease the incidence of these errors by providing usual dose as pre-defined orders and alerts. An important advantage of the CPOE and CDSS is providing evidence-based protocol at default, and therefore standardize the treatment. Nevertheless, we have observed, like reported in other studies [49], that sometimes this theoretical advantage of CPOE may also provoke the prescribing errors since it encourages the healthcare providers to prescribe the usual dose when the patient requires a different dose based on his/her condition or to generate wrong orders due to inflexible ordering format [16]. A recent

systematic review concluded that erroneous decisions following incorrect advice given by CDSS led to an increased risk of commission error [50]. This is known as 'automation bias' in the literature (i.e. tendency to over-rely on automation). When this bias is added to a lack of appropriate medication reconciliation, orders, and mistakes, a cocktail of potential sources of errors is created [41]

To determine the impact of CPOE on the rates of prescribing error, we performed the subgroup analysis of pre-post studies. The risk of 'omission' type error was significantly reduced after the implementation of CPOE. There are several reasons contributed to the reduction in omission after CPOE implementation. First, the reduction in omission might be due to the simplified ordering process with CPOE system. The need for identifying pending orders in a paper chart and then transcribing them as well as sending the order to the pharmacy was eliminated [51]. Secondly, CPOE's built-in support for order sets (collections of clinically-related orders grouped by purpose) could decrease omission error in case clinicians forgot to prescribe. Multiple studies reported that omission of a drug was the most frequently occurring reason for pharmacist's intervention [23]. Proactive attitude of the clinical pharmacists which, as a consequence, led to more 'interfering' interventions [23]. According to our subgroup analysis, neither overall rate of error nor each type of error beside omission was reduced after the implementation of CPOE. This finding could indicate that system-related errors were a major reason for CPOE not delivering a significant reduction in the overall rate of clinical errors.

We are aware that these findings cannot be completely

extrapolated to every setting, mainly due to the particularities of each software and environment. However, the information gathered about these errors and mechanisms responsible for CPOE errors could provide the capture of the prevalence of CPOE-related errors and their types at current state and reveal areas to improve the structure and facilities of CPOE. The system improvement and the appropriate training of prescribers are needed in order to prevent prescribing errors due to CPOE. Numerous types of prescribing error were caused by mechanisms specific to CPOE, such as incorrect selection from the drop-down menu or typographical error. Also, failure to modify the default protocol or setting of CPOE resulted in prescribing errors. The 'wrong dose' errors were caused by the prescribers habitually accept the default dose proposed by the CPOE system without taking the renal function of the patient into account. CPOE does not easily permit the redaction of complex orders, such as corticoids, controlled pump for analgesia, thus targeted training should be strongly encouraged. Technical issues must be resolved beforehand with the software vendor. In one example, overuse of override function in the alert was widely described. Improving the relevance of alerts would decrease the alert fatigue, and as a result, it would decrease the number of alert overrides. Therefore, these systems need to be continually examined and enhanced.

It is important not only to improve healthcare provider's prescribing behavior and technology, but also to strengthen pharmacy validation as secondary defense of preventing the prescribing errors. Ergonomic improvement of the technology cannot completely replace the pharmacist's role in optimizing patient care, but it may allow pharmacists to focus on the most

relevant clinical intervention. The intervention of potential prescribing errors by a clinical pharmacist has decreased the frequency of adverse drug reaction. According to the study of Shulman et al. [52], most of the errors related to CPOE were minor in outcome because they were intercepted and corrected by a clinical pharmacist before it reached the patient. If the error had not been intercepted by the pharmacist, it could have harmed the patient. Bouchand et al. highlighted the important role of pharmacists still have in reducing prescribing errors, despite computerization [18]. Importance of daily prescription review by clinical pharmacists and discussion between healthcare professional should be emphasized [12,42]. It is true that the contribution of technology has increased with the advent of the 4th Industrial Revolution, but users who manipulate technology are still humans and it is difficult to assume that technology is completely error-free, so we should change clinical practice in response to advance in technology to work complement, rather than duplicate, in order to minimize the medication errors.

Our study has several limitations. The large heterogeneity of the prevalence of CPOE-related prescription errors can be explained by structural and organizational differences between the included studies. First, the characteristics of study department within the hospitals, duration of study, adaptation period after the implementation of CPOE, and the total number of prescriptions studied by the authors varied widely. Lower frequency of CPOE-related errors reported in Loustalot et al. study [38] might because the study took place 15 years after the implementation of the software and the medical staffs were fully adapted to the system by the time. This suggests the importance of regular training and the

sharing of knowledge between users of the same CPOE system.

Secondly, the type of software and the level of CDSS used in the studies influenced the percentages of prescribing errors, which has been described in other studies [23,44]. For example, Bouchand et al. [18] implemented two different software in the same setting and the percentage of prescription errors varied from 12.78% to 23.95%.

In third, the definition of prescribing error and the taxonomy used to classify errors were subjective. Although the definitions of error and CPOE-related error were similarly defined throughout the included studies, discrepancies between the performances of pharmacists who identified the errors cannot be excluded such that high levels of inter-individual and intra-individual reproducibility were not ensured. Moreover, identifying errors after the implementation of CPOE presents specific challenges due to the multifaceted nature of the causes, types, certainty, and severity of errors and differences in the ability to detect errors once they have occurred [53].

Lastly, the reported prevalence of the prescribing errors could not reflect the 'true' rate of overall prescribing errors. Seven studies included in our analysis evaluated the records of the pharmacist's intervention on prescribing errors, but the records could contain a certain level of subjectivity and may not be comprehensive. As our study included only pharmacists as one group of healthcare professionals to give uniformity in defining errors, errors detected and corrected by other healthcare professionals such as doctors and nurses could not be investigated and, thereby, the overall error rates from all types of healthcare professionals could not be provided. An error noted by a pharmacist

may not be judged as such by the prescriber and pharmacists can also miss out on some errors or may have not recorded all of their interventions in the system. Thus, the number of errors could have been under- or over-estimated.

Future research is required to conduct the analysis with bigger sample size with higher inter-reliability scores between raters using unified taxonomy to capture more accurate results. Developing more sophisticated CDSS based on the mechanisms responsible for generating errors and enhancing the awareness of healthcare providers regarding the prevalence of prescribing error could all minimize the impact of this problem on the patient safety.

Ⅴ. Conclusion

We conducted the systematic review and meta-analysis to describe the prevalence of CRE and evaluate the association between the implementation of CPOE and the rate of prescribing errors. Our study concluded that CRE occurred approximately 1 in 3 errors and the most frequent type of CRE was wrong dose, followed by wrong drug. There was no significant change in overall rate of prescribing error after the introduction of CPOE, except omission type of error.

In conclusion, a considerable risk for prescribing errors still exists, which shows the importance of involving clinical pharmacy services in multidisciplinary intervention strategy. Healthcare professionals should be aware that CPOE could also lead to a new type of medication error and receive continuous and multidisciplinary training on the use of CPOE and CDSS to reduce the medication errors.

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Appendix

Appendix A. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	i
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	i -iii
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2-3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	50-51
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10-11

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-16
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	17
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	18-27
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	19, 25
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	20, 21, 26
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	24-27
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	28-32
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	32-34
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	35
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	None

Appendix B. Search Strategy

PubMed	
#1	"Medical Informatics"[Mesh] OR "Public Health Informatics"[Mesh] OR "medical order entry systems"[Mesh] OR "health informatics"[all fields] OR "health information technology"[all fields] OR "computerized physician order entry system"[all fields] OR "CPOE"[all fields]
#2	"Medication errors"[Mesh] OR "Prescribing errors"[all fields]
#3	"Pharmacy"[Mesh] OR "Pharmacies"[Mesh] OR "Clinical Pharmacy Information Systems"[Mesh] OR "Pharmacists"[Mesh]
#4	#1 AND #2 AND #3
EMBASE	
#1	(‘clinical information system’/exp OR ‘pharmacy’/exp OR ‘pharmacist’/exp) AND ([article]/lim OR [review]/lim)
#2	('computerized provider order entry'/exp OR 'computerized physician order entry' OR 'order entry' OR 'order-entry' OR 'cpoe' OR 'medical order entry systems' OR 'medical informatics'/exp OR 'health information technology'/exp OR 'computer assisted drug therapy'/exp OR 'medical technology'/exp) AND ([article]/lim)
#3	'medication errors'/exp OR 'prescribing errors'
#4	#1 AND #2 AND #3
Cochrane	
#1	MeSH descriptor: [Medical Informatics] explode all trees
#2	MeSH descriptor: [Medical Order Entry Systems] explode all trees
#3	‘Health information technology’
#4	‘Health informatics’
#5	‘Computerized Physician Order Entry System’
#6	‘CPOE’
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	MeSH descriptor: [Pharmacies] in all MeSH products
#9	MeSH descriptor: [Pharmacists] explode all trees
#10	MeSH descriptor: [Clinical Pharmacy Information Systems] explode all trees
#11	#8 OR #9 OR #10
#12	MeSH descriptor: [Medication Errors] explode all trees
#13	‘Prescribing errors’
#14	#12 OR #13
#15	#7 AND #11 AND #14
Scopus	
#1	((KEY("medical informatics") OR KEY("medical order entry system") OR TITLE-ABS-KEY("health informatics") OR TITLE-ABS-KEY("health information technology") OR TITLE-ABS-KEY("computerized provider order entry system") OR TITLE-ABS-

	KEY("CPOE")))
#2	((KEY("pharmacy") OR KEY("pharmacies") OR KEY("pharmacists") OR TITLE-ABS-KEY("clinical pharmacy information systems")))
#3	((KEY("medication errors") OR TITLE-ABS-KEY("prescribing errors")))
#4	#1 AND #2 AND #3

Appendix C. Taxonomy of prescribing errors

Definition	Example[a]
Omission	
• Untreated indication • Failure to receive drug	*Potassium omitted for a patient with hypokalemia*
Wrong drug	
• Drug without indication • Duplication of therapy (same drug or drug in same therapeutic class) • Prescription of drug to which patient has a history of significant allergy • Prescription of drug to which patient has clinical contraindication (drug-disease interaction) • Prescription of drug that is contraindicated due to drug interaction (drug-drug interaction) • Continuing a drug in the event of a clinically significant adverse drug reaction	*Fluticasone/salmeterol inhaler prescribed for a patient without chronic obstructive airways disease* *Hydrocortisone 25mg was prescribed instead of cortisone* *Ranitidine and omeprazole for gastroesophageal reflux disease*
Wrong dose	
• Dosage regimen (strength, frequency, unit, quantity) selection error • Overdose/underdose	*Microgram was selected instead of milligram* *Alendronate 75mg PO 1T qw when weekly dose only available in 70mg* *Everolimus 0.25mg, 0.25 tablet prescribed when intended dose was one 0.25mg tablet*
Wrong route/form	
• Wrong or inappropriate route	*OS (left eye) was prescribed instead of OD (right eye)* *IV medication was prescribed orally*

• Wrong or inappropriate formulation	*An immediate release tablet was prescribed when an extended release form was required*
Wrong time	
• Premature discontinuation • Failure to stop treatment • Failure to renew treatment • Prescribed administration times incorrect • Incorrect start date/end date	*Simvastatin prescribed in the morning instead of the evening*
Wrong patient	
• Prescription of a drug for the wrong patient by unintentionally choosing the wrong patient's page on the system/wrong patient's medication chart	
Monitoring error	
• Prescriber fails to order appropriate and timely clinical or laboratory tests to assess the patient's response to prescribed therapy	*Missing warfarin check (INR)*

Appendix D. Newcastle–Ottawa Scale (NOS) for assessing the quality of observational studies

Study	Selection				Comparability	Outcomes			Rating[g]
	Representativeness of exposed cohort[a]	Selection of the non-exposed cohort[b]	Definition of PE	Definition of CRE	Comparability of Cohort[c]	Blinding[d]	Adequate period[e]	Adequate sample[f]	
Abdel-Qader et al. [23]	★	★	★	★	★ ★	★	★	★	Good
Alhanout et al. [31]	–	★	–	–	★	–	–	★	Poor
Estellat et al. [33]	★	★	★	★	★	★	★	★	Good
Hellot-Guersing et al. [34]	★	★	★	★	★	–	★	★	Good
Loustalot et al. [35]	★	★	★	★	★ ★	–	★	★	Good
Raimbault-Chupin et al. [36]	★	★	★	–	★	–	–	–	Fair
Velez-Diaz et al. [38]	★	★	–	–	★ ★	–	★	★	Fair
Vialle et al. [39]	★	★	–	–	★	–	★	★	Fair
Villamanan et al. [40]	★	★	★	★	★	–	★	–	Fair
Westbrook et al. [42]	★	–	–	★	★ ★	★	★	★	Good

[a]Study represented exposed individuals in the community, not the selected group of users; [b]Sample includes all patients within selected departments; [c]Study included clear methods with multiple trained reviewers to identify prescribing errors (one point) and performed inter-rater reliability test (two points); [d]Reviewers were independent from the hospital or hospital staff were unaware of the study; [e]Data collection period was reported and, where applicable, allowed for a minimum 6 month adaptation period after implementation of the system; [f]Study included an adequate sample (at least 300 orders, reports, intervention, and errors) [i]Good:7-9stars, Fair:4-6 stars, Poor:0-3 stars

국문초록

처방자동화시스템(Computerized Physician Order Entry, CPOE)과 임상의사결정지원시스템(Clinical Decision Support System)의 활성화로 전체적인 처방오류의 비율은 감소하였지만, CPOE와 같은 새로운 시스템으로 인하여 새로운 오류가 출현되었다. 본 연구는 원내 CPOE와 관련된 약물 처방오류 중 약사가 평가한 처방오류의 발생률과 CPOE 도입 전후 오류유형의 변화를 파악하고자 선행연구들을 대상으로 체계적 문헌고찰과 메타분석을 수행하였다.

PubMed, EMBASE, Cochrane Register of Controlled Trials, Scopus에서 2020년 3월까지 검색되는 문헌 중 CPOE 도입 후 발생한 처방오류에 해당하는 문헌을 추출하였고 선정 및 제외기준에 따라 총 14개의 최종 문헌을 선정하였다. 처방오류의 합동 발생률 수치와 CPOE 도입 전과 후 유형 별 처방오류 발생의 상대 위험도 및 95% 신뢰구간은 랜덤 효과 모델을 적용하여 제시하였다.

CPOE 도입 후 전체 처방오류 중 CPOE로 인한 처방오류의 발생률 추정치 범위는 12.78%에서 58.54% 사이였고 랜덤 효과 모델에서 계산된 합동 발생률은 32.36%였다 (95% 신뢰 구간 22.87-42.62). National Coordinating Council for Medication Error Reporting and Prevention 분류체계에 기반하여 문헌에서 추출 가능한 처방오류의 유형을 “처방 누락오류”, “약물 오류”, “용량오류”, “제형 및 투여경로 오류”, “투여 시간 오류”, “약물 모니터링”과 같이 총 6개 유형으로 분류하였을 때, 용량오류가 47.28% (95% 신뢰구간 38.38-56.26)로 가장 높았고 그 다음은 약물 오류가 14.45% (95% 신뢰 구간 7.96-22.40)으로 높았다. CPOE 도입 전과 후의 처방오류 유형별 발생을 비교하기 위하여 하위그룹 메타 분석을 하였을 때, CPOE 도입 후 전체적인 처방오류의 발생률은 CPOE 도입 전에

비해 통계적으로 유의하게 증가하지 않았으나 (Relative risk, RR 0.842, 95% 신뢰 구간 0.559-1.168), 6개 처방오류 유형 중 메타분석이 가능한 5개 오류 유형 중 (처방 누락오류, 약물 오류, 용량오류, 제형 및 투여경로 오류, 약물 모니터링) 처방 누락오류만 CPOE 도입 후 유의하게 줄어들었다 (RR 0.484, 95% 신뢰 구간 0.282-0.831).

체계적 문헌고찰 및 메타분석을 통해 새로운 기술인 CPOE 도입 후 CPOE와 관련된 처방오류가 전체 처방오류 중 1/3의 빈도로 발생하는 것으로 파악되었다. 처방오류의 유형 중 처방 누락오류, 약물 오류, 용량오류, 제형 및 투여경로 오류, 약물 모니터링의 오류의 발생 비율은 CPOE 도입 전과 후에 유의한 변화를 보이지 않았으나, 처방 누락의 비율은 CPOE 도입 후에 낮아진 것으로 나타났다. 약물처방의 전자화와 처방 지원 시스템과 같은 새로운 기술의 도입으로 단순 실수로 인한 처방오류는 방지되었으나 다양한 처방오류가 지속해서 발생함으로 환자의 안전을 위한 시스템 사용자의 지속적인 교육과 시스템의 기술적 개선으로 처방오류의 예방, 감지, 및 모니터링의 노력이 필요하다.

주요어 : computerized physician order entry system, prescribing error, pharmacist
학 번 : 2018-21399